

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 007541-000005									
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____ Signature _____ Typed or printed name _____	Application Number 10/561,529	Filed December 20, 2005									
	First Named Inventor Samaritani, Fabrizio										
	Art Unit 1647	Examiner Stoica, Elly-Gerald									
<p>Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.</p> <p>This request is being filed with a notice of appeal.</p> <p>The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.</p> <p>I am the</p> <table style="width: 100%; border: none;"><tr><td style="width: 50%; vertical-align: top; padding: 5px;"><input type="checkbox"/> applicant/inventor.</td><td style="width: 50%; vertical-align: top; padding: 5px;"><u>/Thomas Q. Henry, Reg. No. 28309/</u> Signature</td></tr><tr><td style="vertical-align: top; padding: 5px;"><input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)</td><td style="vertical-align: top; padding: 5px;"><u>Thomas Q. Henry</u> Typed or printed name</td></tr><tr><td style="vertical-align: top; padding: 5px;"><input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>28309</u></td><td style="vertical-align: top; padding: 5px;"><u>(317) 634-3456</u> Telephone number</td></tr><tr><td style="vertical-align: top; padding: 5px;"><input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____</td><td style="vertical-align: top; padding: 5px;"><u>June 8, 2009</u> Date</td></tr></table> <p>NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.</p>				<input type="checkbox"/> applicant/inventor.	<u>/Thomas Q. Henry, Reg. No. 28309/</u> Signature	<input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)	<u>Thomas Q. Henry</u> Typed or printed name	<input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>28309</u>	<u>(317) 634-3456</u> Telephone number	<input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____	<u>June 8, 2009</u> Date
<input type="checkbox"/> applicant/inventor.	<u>/Thomas Q. Henry, Reg. No. 28309/</u> Signature										
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<input checked="" type="checkbox"/> *Total of <u>1</u> forms are submitted.											

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/561,529
Confirmation No.: 9788
First-Named Inventor: Fabrizio Samaritani
Filing Date: December 20, 2005
Group Art Unit: 1647
Examiner: Elly-Gerald Stoica
Attorney Docket No.: 7541-5
Title: FREEZE-DRIED FSH/LH FORMULATIONS

REMARKS FOR PRE-APPEAL BRIEF REVIEW

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

These Remarks for Pre-Appeal Brief Review are being filed along with a Pre-Appeal Brief Request for Review (PTO/SB/33) and Notice of Appeal (as well as associated fees). No Appeal Brief has yet been filed. A Petition for a Two Month Extension of Time, and the accompanying fee, are also submitted herewith.

The Commissioner is authorized to charge any additional extensions of time as well as any additional fees or credit any overcharges to Deposit Account No. 23-3030, but not to include any payment of issue fees.

Status of the Claims

The Final Office Action in this case was mailed on January 7, 2009 (the "Final Action"), and a Response To Final Office Action was submitted on March 9, 2009 (the "Response To Final"). An Advisory Action was mailed on March 20, 2009 (the "Advisory Action"), indicating that the Response To Final would be entered for purposes of appeal, and rejecting the claims. These Remarks are therefore based on the claims as amended in the Response To Final.

Claims 46-51 and 55-60 are pending in the case. All of the claims relate to freeze-dried formulations ***consisting of*** follicle stimulating hormone ("FSH") and luteinising hormone ("LH"), and certain other components. Claims 46 and 55 specify FSH, LH, and a phosphate buffer, and generally identify a surfactant (polyoxyethylene (20) sorbitan monolaurate,

polyoxyethylene (20) sorbitan monopalmitate or polyoxyethylene (20) sorbitan monooleate), a stabilizer/tonicity agent (monosaccharides, disaccharides or sugar alcohols), and an antioxidant. The other claims also specify FSH, LH and a phosphate buffer, but more specifically identify polyoxyethylene (20) sorbitan monolaurate, sucrose and methionine as the additional components. Claims 47-51 and 56-59 require recombinant FSH (“rFSH”) and recombinant LH (“rLH”).

All of the claims have been rejected as unpatentable over U.S. Patent No. 5,384,132 to De Meere et al. (“De Meere”) and European Patent Application No. EP 0 853 945 to Skrabanja et al. (“Skrabanja”).

Background

There has been a long-standing recognition of the difficulty in preparing stable FSH, and particularly rFSH, formulations:

“The stability of proteins in aqueous formulations is generally a problem in [sic] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer [sic] times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods.” **Skrabanja**, page 2, lines 42-45.

See also DeMeere, col. 1, lines 30-37 and col. 2, lines 53-58. Stability is even more problematic for formulations including both FSH and LH:

“A need exists for a gonadotropin containing pharmaceutical preparation which is stable over a sufficiently long period of time for the product to be manufactured, shipped, and stored prior to use. The need is especially great for a stable preparation containing more than one gonadotropin.” **De Meere**, col. 1, lines 38-43.

In contrast, applicants have found that formulations according to the present claims provide surprising stability, even for rFSH and rLH, and without the need for additional stabilizers. In particular, the present invention avoids the use of a polycarboxylic acid, or salt thereof, as required by the cited art.

The Claim Rejections

The claims have been rejected as being unpatentable over De Meere, taken alone or in view of Skrabanja.

De Meere

De Meere describes gonadotropin formulations including a “dicarboxylic acid salt stabilizer”:

“Generally, the invention includes a gonadotropin containing lyophilized protein preparation which contains a *dicarboxylic acid salt stabilizer*. . . . The preparation will contain a sufficient amount of dicarboxylic acid salt to stabilize the gonadotropin in its freeze-dried form for a desired time at a desired temperature.” **De Meere**, col. 1, lines 46-56 (emphasis added).

De Meere further teaches that formulations without the dicarboxylic acid salts are not stable. In Example I, De Meere describes the preparation of two FSH samples with the difference (other than the concentration of the Tween 20) being that the first sample included sodium citrate and the second did not. The results indicate the instability of the FSH formulation in the absence of sodium citrate:

“The first sample is stored for 3 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed little oligomer formation. The second sample, not containing sodium citrate, was stored for 6 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed much more oligomer formation.

The profile of the first sample showed no degradation products while the profile of the second sample showed *almost exclusively oligomeric products*.” **De Meere**, col. 6, lines 45-56 (emphasis added).

Skrabanja

Skrabanja describes formulations including FSH, LH and/or other gonadotropins which utilize a dicarboxylic acid, or salt thereof, for stabilization. Skrabanja more specifically discloses the use of a thioether compound to improve the stability achieved with the polycarboxylic acid/salt:

“The invention relates to a liquid gonadotropin-containing formulation which comprises a gonadotropin and *stabilizing amounts of a polycarboxylic acid or a salt thereof* and of a thioether compound. The gonadotropin-containing formulations of the invention have improved stability on prolonged storage in comparison with formulations in which the thioether compound is lacking.” **Skrabanja**, page 3, lines 15-18 (emphasis added).

Basis for the Review Request

1. The Office Actions have failed to adequately address the “consisting of” language.

In the Final Action, the Examiner rejected previous “consisting *essentially* of” claims by stating:

“If Applicant wants to specifically exclude the citric acid containing formulation [sic] should do so explicitly by choosing the limiting term consisting of.” Final Action, p. 5, lines 17-19.

However, then-pending claims 46-49 did include that term, but the Final Action did not address it. Instead, the Final Action mischaracterized claims 46-49 as “comprising” the listed components. See, Final Action, p. 7, lines 1-3.

It is apparent that the Final Action did not deal with the “consisting of” term, but rather treated the claims as “comprising” claims. In rejecting claims 46-49, the Final Action stated:

“Adjusting the actual quantities of the ingredient it [sic] was therefore considered routine in the art. Therefore it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of De Meere et al. and Skrabanja et al. to optimize the quantities with a reasonable expectation of success.” **Final Action**, p. 7, lines 14-18.

The Final Action does not purport to explain how removal of the polycarboxylic acid/salt could amount simply to “adjusting” or “optimizing” the ingredients of De Meere or Skrabanja when both references are based on its use. The Final Action therefore did not meaningfully address the fact that claims 46-49 used the term “consisting of.”

In applicants’ Response To Final, the claims were amended to include the term “consisting of” in all of the claims. In the Advisory Action, the claims were again rejected with no discussion of issues relating to use of the “consisting of” term.

The rejections of the claims fail to address the significance of the “consisting of” language, and are therefore legally deficient on that basis.

2. Failure to show a proper motivation for modification of the art in a §103 rejection.

All of the pending claims use the transitional phrase “consisting of”. This phrase has a clearly understood meaning in patent claims - that the invention includes the listed components and no others. By comparison, the cited art fails to disclose or suggest an FSH/LH formulation limited to the claimed components. More particularly, the cited references teach the inclusion of polycarboxylic acids, or salts thereof, to provide stable formulations.

The Final Action and Advisory Action do not articulate a sufficient basis for the conclusion that a person combining the teachings of De Meere and Skrabanja would have made the claimed invention. The De Meere and Skrabanja references both focus on the difficulty in providing stable FSH formulations, and claim to have solved this problem by the use of a polycarboxylic acid, or salt thereof. Without this stabilizer, DeMeere obtained “almost exclusively oligomeric products.” De Meere, col. 6, lines 45-56. It is factually insufficient to state that the present invention is simply adjusting or optimizing the ingredients in the prior art. Both De Meere and Skrabanja not only disclose the use of polycarboxylic acids, or salts thereof, but they both indicate that the use of such acids/salts is the basis for the stabilization of their formulations. The Final Action and the Advisory Action have a clear fact deficiency in failing to rationalize how one skilled in the art would expect to prepare a stable FSH/LH formulation by modifying the art to remove the stabilizing component from each.

3. rFSH and rLH claims are further distinguished over the art.

Claims 47-51 and 56-59 are directed to formulations which include recombinant, human FSH and LH. The cited art indicates that stability of highly pure, rFSH and rLH is even more difficult to accomplish. The significance and novelty of the present invention is therefore even greater with respect to the formulations covered by those claims.

Conclusion

It is respectfully requested that the bases for the final rejections of the pending claims be reviewed. If there are any questions or comments that would speed the prosecution, the Office is requested to contact the undersigned by telephone to quickly resolve any issues.

Respectfully submitted,

June 8, 2009

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